REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

A. Amendments to the Claims.

Claims 9, 10 and 13 are requested to be cancelled.

Claims 1, 12 and 17 are currently being amended.

Claim 18 is being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. For ease of reference, a clean set of the claims without markups is appended hereto.

After amending the claims as set forth above, claims 1-8, 11-12 and 14-18 are now pending in this application. No new matter is added to the application by the amendment of Claim 1 to include the limitation that the targeted neurons are "neurotrophin-responsive" ones; by the amendment of Claim 12 to incorporate the subject matter of Claim 13, and other material, into a Markush grouping; or by the addition of new Claim 18.

In particular, the amendment of Claim 1 is supported by the description in the specification at page 4, lines 10-20 (as to the "neurotrophin-responsive" limitation), as well as by the text of the original claim (e.g., as to the "10 mm" limitation). The amendment of Claim 12 is supported by the description in the specification at page 7, line 14 through page 8, line 4, as well as original Claim 13, now cancelled. Further, newly added Claim 18 is fully supported by the description in the specification at page 4, lines 16-20.

Entry of the foregoing amendments is therefore requested.

B. Response to Rejection of Claims 1-17 Under Section 112, First Paragraph (Written Description).

The claims are rejected as not being enabled for delivery of neurotrophins other than NGF. Applicant respectfully disagrees.

First, Applicant notes that, based on an identical disclosure, claims to the delivery of any neurotrophin into the brain according to the invention have already been allowed, such that the issue of whether the specification provides adequate written description of that aspect of the claimed invention has already been decided in Applicant's favor. For example, Claim 1 of the parent application, now U.S. Patent No. 6,683,058, reads as follows (with emphasis added) with respect to *in vivo* delivery:

> 1. A method for delivery of **a therapeutic neurotrophin** to one or more defective, diseased or damaged cholinergic neurons in the mammalian brain, the method comprising **directly delivering a neurotrophic composition, comprising a neurotrophin encoding transgene,** into one or more delivery sites within a region of the brain containing targeted neurons, whereby the transgene is expressed in, or within 500 .mu.m from, a targeted cell, and no more than about 10 mm from another delivery site; and wherein contact between the targeted cell and the neurotrophin ameliorates the defect, disease or damage.

Applicant submits that the interests of consistent prosecution require that claims directed to the delivery of neurotrophins according to the invention into the brain be considered to be supported by the present disclosure. See, e.g., MPEP 706.04:

> "Full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner, or make a new search in the mere hope of finding something. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 139, 57 USPQ2d 1449, 1499-50 (D. Mass. 2001)."

Applicant respectfully submits that the previous Examiner's determination that the written description of the claimed invention meets the requisites of Section 112, first paragraph was correct, and is compelled by both the disclosure and the state of the art at the time the invention was made.

The invention pertains to a method for delivering neurotrophins to neurons in the brain that are responsive to them, in the sense that the neuron responds by growing or displaying activity. The activity of neurotrophins such as those described at page 7, line 14 through page 8, line 4 of the specification, as well as the identity of neurons responsive to each in the brain, is and was well-known to the art (see, e.g., References A (U.S. Patent No. 5,762,926, at Col. 12, lines 44-50 and Col. 12, line 65 through Col. 13, line 10); neurotrophins useful in stimulating tropic or trophic neuronal responses in the brain include NGF, NT-3, NT-4 [now known as NT-4/5], CNTF, BDNF and others), A33 ((NGF stimulation of forebrain neuronal growth in monkeys), A35 (BDNF maintains activity among dopaminergic neurons in the brain), A42 (NGF responsive neuronal loss in Alzheimer's Disease [AD]), A43 (NGF responsive neuronal loss in Parkinson's Disease); Lapchak, *et al.*, *Brain Res.*, 777:153-160, 1997 (enclosed; adenovirally delivered GDNF stimulates dopaminergic neuronal function); and, Yan, *et al.*, *Exp.Neurol.*, 127:23-26, 1994 (enclosed; distribution of receptors for NGF, NT-3 and BDNF in the forebrain and striatum). The common identifying characteristic of relevance for these neurotrophins is that each exerts a trophic or tropic influence on neurons in the mammalian brain, a fact disclosed in the specification (and otherwise well-known in the art).

The comments in the Office Action regarding the Interim Guidelines' statements concerning description of a genus by reference to a single species is not apt in this instance. Here, the genus of neurotrophins that exert a trophic or tropic effect on neurons in the brain are exemplified by reference to a variety of species which possess those characteristics (see, e.g., Specification; e.g., at page 7, line 14 through page 8, line 4).

As noted above, those of ordinary skill in the art at the time the invention was disclosed would have been familiar with the characteristics of such neurotrophins, as well as with the distribution of receptors therefore in the brain. As such, an exhaustive recitation of the identity and/or activity of all of the neurotrophins useful in the invention was not necessary to provide an adequate written description of the invention. Instead, the written description requirements of Section 112, first paragraph, are satisfied if "one of ordinary skill in the art could have combined the [disclosure's] description of the invention with his own knowledge to make the claimed invention." *In re Donohue,* 226 USPQ 619 (Fed.Cir. 1985). As such, an inventor "does not need to include in the specification that which is already known to and available to one of ordinary skill in the art," to whom the specification is addressed. *Koito Manufacturing Co. Ltd., et al. v. Turn-Key-Tech, LLC.,* 381 F.3d 1142, 1155 (Fed.Cir. 2004), citing *Paperless Accounting, Inc. v. Bay Area Rapid Transit System,* 804 F.2d 659, 664 (Fed.Cir. 1986); *In re Lange*, 644 F.2d 856, 863 (CCPA 1981), and *In re Gay*, 309 F.2d 769, 774 (CCPA 1962).

Moreover, the instant claims to a method of delivering neurotrophins are not comparable to those addressed in the cited portions of the Interim Guidelines, or by the *Fujikawa* and *Vas-Cath* cases, each of which involved claims to compositions of matter exemplified in the disclosures at issue by a limited number of disclosed structural variations. In such a claim, it is important for the artisan to be advised of "complete or partial structure, physical or chemical properties, functional characteristics, structure/function correlation," etc. (Office Action at page 3, second paragraph) so unknown structural members of the claimed genus can be identified. In contrast, the members of the neurotrophin genus for use in the invention, and their individual utilities in stimulating growth by, or activity in, mammalian neurons, is both disclosed in the specification and well-known in the art.

For all of these reasons, Applicant submits that the rejection of the claims as lacking written description support should be withdrawn.

B. Response to Rejection of Claims 1-17 Under Section 112, First Paragraph (Enablement)

The enablement rejection set forth in the Office Action appears to be based upon the conclusion that the data set forth in the specification only supports claims to the *ex vivo* practice of the invention; i.e., "grafting genetically modified fibroblast cells comprising an adeno-associated viral vector expressing NGF intraparenchymally to the basal forebrains of monkeys and increasing expression of p75 in cholinergic neurons in the basal forebrain." Applicant respectfully disagrees. The allowance of the *in vivo* claims referenced above in the parent application indicates that the question of whether the *in vivo* practice of the invention is enabled by the disclosure has already been decided in Applicant's favor. As provided under MPEP 2124, that decision should be given "full faith and credit" with respect to the present *in vivo* method claims.

In regard to the *in vivo* practice of the invention, the Examiner's attention is respectfully drawn to the data provided in the Specification regarding the delivery of neurotrophins via direct introduction of a transgene-encoding AAV vector into the brain (see, Example II, page 20). All of the experiments reported were conducted in animal models of neuronal cell death, similar to that which occurs in conditions such as Alzheimer's Disease (see, e.g., Example III and Example II, both of which utilized the fornix transection model described in the Specification, at page 17, lines 6-26, as being clinically relevant to conditions involving such neuronal cell death). As stated in the Specification, "[t]hose of ordinary skill in the art will appreciate that while the Examples illustrate an ex vivo application of the invention, the results achieved will be accessible through in vivo delivery..." (Specification at page 18, lines 3-5).

Indeed, the invention has enjoyed an unprecedented measure of "real world" success. In this respect, enclosed for the Examiner's reference are a Declaration under Rule 1.132 of the inventor (originally submitted in the parent application) with respect to the successful use of the invention in primate animal models of AD and PD, as well as a recent report concerning the clinical trial application of the invention (*ex vivo* approach—an *in vivo* trial is underway) for

treating AD in humans (see, Tuszynski, *et al., Nat. Medicine,* 11:551-555, 2005, enclosed; results regarding a trial for treating PD are also reported therein at 553, second column). The results of these trials confirm that the reasonable expectation in the art as of the priority date in the invention's ability to stimulate neuronal growth and activity was well justified.

In particular, Dr. Tuszynski's Declaration confirms the results of two sets of experiments using the *in vivo* technique claimed herein in aged animals, as well as art-accepted animal models of Alzheimer's (AD) and Parkinson's Disease (PD) (both non-human primates and rodents were utilized). In these experiments, expression was not only of sufficient volume (> 90% of neurons targeted were transfected) and duration (8+ months, at last testing) to offer a therapeutic benefit to treated animals, a demonstrable improvement in motor function and cognition was confirmed. See, e.g., data presented in Tuszynski Declaration, at 3, 6, 12, 14-21 and 25-29.

Expression in these animals persisted throughout the test period (in excess of 8 months for several animal sets). Although expression may decline over time, the expression which is achieved is sufficient to treat, and possibly even reverse, the cognitive and motor function impairment observed in the test animals. Tuszynski Declaration, at 3. Moreover, these results were achieved without detectable inflammation in the brain. Tuszynski Declaration at 4, 6 and 12.

In the human clinical trials, responses to expression of exogenous neurotrophin in the brain have been remarkable. For example, the rate of progression of AD in the first patient treated is estimated to have been slowed by upwards of 51%, a heretofore unprecedented result in treatment of AD (Tuszynski, *et al.*, at 553, first column). The therapeutic benefits of the invention may therefore not only mitigate the effects of diseases such as AD on the brain, but also offers a chance to improve the quality of life for sufferers to an extent that could, for example, delay the time when skilled nursing care becomes necessary. The invention therefore represents a truly extraordinary achievement in the treatment of human disease.

For the contrary position, the Office Action relies on three references published in 2004 (Counts, *et al.*, Rogawski, and Reichardt) as evidencing lack of enablement[1]. However, none of the references indicate that those of ordinary skill in the art that the invention cannot be practiced as claimed; to the contrary, in many respects, they individually and collectively compel the opposite conclusion.

The Rogawski teaching relating to treatment of cognitive impairment in AD patients with a composition that does not inhibit cholinesterase does not, contrary to the conclusion stated in the Office Action, in any way teach that cholinergic neuronal density and activity is not impaired in such patients, a fact that is well-accepted in the art. Indeed, the role of cholinergic neuronal loss is acknowledged by Rogawski (see, e.g., the text box on page 6 of the reference: "acetylcholine (ACh)-containing neurons are particularly vulnerable in AD.").

It will be appreciated that the invention is not claimed as a cure for any disease, but as a means to stimulate neuronal growth and activity, functions that are lost during neurodegeneration resulting from a variety of conditions, including AD (cholinergic neuron activity loss), Parkinson's (dopaminergic neuron activity loss) and even the process of normal aging. Hence, the possibility that processes other than neuronal loss or inactivity may also accompany the course of any particular disease state or condition (as alluded to by Rogawski) is not pertinent to whether the loss or inactivity is addressed by the invention.

With respect to the Reichardt reference, Applicant respectfully submits that the Examiner has misread it in concluding that it teaches "only NGF supports survival and differentiation, NT-3 does not." (Action at page 7, second paragraph). What the reference actually says is that

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[1] In this respect, it will be appreciated that enablement is judged by the understanding of those of skill in the art at the time that the invention was made (by the priority date), not at a subsequent time. Thus, post-invention art (other than review articles describing the state of the art when the invention was made) cannot be used to support a *prima facie* case for lack of enablement. See, MPEP 2124: "[I]t is impermissible to use a later factual reference to determine whether the application is enabled or described as required under 35 U.S.C. 112, first paragraph. In re Koller, 613 F.2d 819, 823 n. 5, 204 USPQ 702, 706 n.5 (CCPA 1980)." Without acquiescing in the citation of the post-invention references in the Office Action, Applicant's substantive response thereto is set forth herein for the purpose of expediting prosecution of the pending claims.

"[w]hile both enhance axon growth, only NGF signals *retrogradely* to support survival and differentiation." (Reichardt, at 142, second column, emphasis added). In other words, NT-3 and NGF both act on neuronal axons (anterograde activity), but their data indicated that NGF also acted on the cell body (retrograde activity), whereas NT-3 did not. The authors speculate that "NT-3 might ensure survival of neurons during axon growth while NGF would take over this role once axons reached their target." (*Id.*, first column). Because axonal growth is important in increasing neuronal activity in the brain, Reichardt confirms, rather than negates, the usefulness of both NGF and NT-3 in the invention.

With respect to the question of whether neurotrophins other than NGF (or NT-3) may be utilized in the invention, Applicant respectfully submits that the question has been resolved, both in the art (see, e.g., the discussion at pages 5-7 above) and with respect to the invention in particular (e.g., in the prosecution and allowance of claims in the parent application, now the 6,683,058 Patent). The record is devoid of support for the Office Action's contrary statement that the "signaling effects of different neurotrophins" is unpredictable (Action, at page 7, second paragraph), excepting the Reichardt reference which, as noted above, has been misconstrued.

Lastly, the mention by Counts, *et al.* of p75 expression as remaining stable in the AD brain is not pertinent to the present disclosure, in which increased p75 expression was correctly utilized as a reference point to indicate neuronal growth, and not as an marker for progression of disease.

Based on the foregoing, Applicant submits that the rejection of the claims as lacking enablement should be withdrawn.

C. Response to Rejection of Claims 1-17 under Section 112, Second Paragraph.

The phrase "further contact with the neurotrophin" in original Claim 1 is objected to as vague. Applicant notes that this same language appears in previously issued claims (see, e.g., the '058 Patent), and submits that its meaning is clear. However, in the interest of expedited

prosecution, Claim 1 has been amended. Applicant submits that the amendment of Claim 1 renders this objection moot.

The phrase "greater than or equal to 3 minutes" in original Claim 9 is objected to as vague. Applicant notes that this same language appears in previously issued claims (see, e.g., the '058 Patent), and submits that its meaning is clear. However, in the interest of expedited prosecution, Claim 9 has been cancelled. Applicant submits that the cancellation of Claim 9 renders this objection moot.

The phrase "less than or equal to 10 minutes" in original Claim 10 is objected to as vague. Applicant notes that this same language appears in previously issued claims (see, e.g., the '058 Patent), and submits that its meaning is clear. However, in the interest of expedited prosecution, Claim 10 has been cancelled. Applicant submits that the cancellation of Claim 10 renders this objection moot.

D. Response to Double Patenting Rejection.

Claims 1-17 are objected to as "same invention" double patenting, in view of their issuance in the '058 Patent. Applicant submits that this rejection is moot in view of the amendments to the pending claims.

However, Applicant recognizes that the rejection may be renewed as one for obviousness-type double patenting. In the interest of expedited prosecution, a terminal disclaimer with respect to the term of any patent issued on the instant application extending beyond the term of the '058 Patent is submitted herewith.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 7-19-05

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